This Month in Genetics

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Neurocognitive Effects of Sickle Cell Anemia

Because of medical intervention, sickle cell anemia (SCA), once a fatal pediatric disease, is now a chronic condition. Beyond the pain crises and infarctions that are the obvious manifestations of the disease, there is evidence, at least in pediatric SCA patients, for impaired neurocognitive function in affected individuals. A newly published study compared neuropsychological function in neurologically normal adults with SCA and in control individuals with hemoglobin AA. The results indicate that adults with SCA scored significantly lower on measures of performance IQ, in addition to scoring lower for measures of processing speed, working memory, and executive function. Anemia was associated with the decline in neurocognitive performance, leading the authors to suggest that hypoxic dysfunction is central to this decline. If this holds true, improving blood flow and oxygenation to the brain, possibly even through transfusion, could be a way of intervening to moderate this long-term issue in SCA.

Vichinsky et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA 303, 1823–1831.

Extracting Meaning from the Genome

It seems quite space-age to me, the idea of being presented with your whole genome sequence and having a team of geneticists decipher its meaning for you. But for some lucky guy, this scenario is true, and the results are reported in *The Lancet* by Ashley et al. for all the world to see. As sequencing capabilities have exponentially increased over the past few years, the hurdle to personal genome testing is not in collecting the data but in its interpretation. This research group took a genome sequence and made an attempt to interpret it on the basis of current literature and in conjunction with the individual's personal and family history, which included vascular disease and sudden death. Although the team focused their efforts on three areas—variation in genes for Mendelian disease, SNPs previously associated with complex disease, and pharmacogenetically relevant genes—a team of scientists spent hundreds of hours with the interpretation of this one genome. This included the development of a novel approach to the integration of information at multiple polymorphisms for use in predicting complex disease. Beyond being interesting simply for the information contained within, the analysis of this genome allows the authors to highlight some areas of limitation in our ability to interpret whole-genome information and to suggest approaches that could facilitate the closure of these gaps in knowledge and interpretation. As discussed in an accompanying Viewpoint by Ormond et al. (doi: 10.1016/S0140-6736(10)60599-5), the process of delivering whole-genome information back to the consumer must be streamlined before personal genome sequencing is rolled out into wider use for clinical application.

Ashley et al. Clinical assessment incorporating a personal genome. The Lancet 375, 1525–1535.

A Show of Talents from Optineurin

Although its original claim to fame was that mutations in this gene cause adult-onset primary open-angle glaucoma, optineurin has proven to be a multitalented protein. This negative regulator of NF-κB is involved in vesicle trafficking and maintenance of the Golgi through its association with myosin VI, and it has recently been implicated as a critical player in the innate immune response to viruses. But this is not the whole story for optineurin—two recent papers implicate the *OPTN* gene in two very distinct disorders: amyotrophic lateral sclerosis (ALS) and Paget disease of the bone. Maruyama et al. report three *OPTN* mutations in patients with ALS. At least two of these mutations render optineurin incapable of downregulating NF-κB activation. Furthermore, neurons from patients with ALS, even those without *OPTN* mutations, seem to have intracytoplasmic inclusions that contain optineurin. Albagha et al. did a genome-wide association study for Paget disease, a disorder of bone remodeling, and pulled out a SNP within *OPTN*, as well as one near *TNFRSF11A*, which encodes a receptor activator of NF-κB (RANK). The role of optineurin in regulating NF-κB might be the link tying all of these functions together, but it seems as though this protein still has some talents that we have yet to uncover.

Albagha et al. Genome-wide association study identifies variants at CSF1, OPTN, and TNFRSF11A as genetic risk factors for Paget's disease of bone. Nature Genetics. Published online May 2, 2010. 10.1038/ng.562.

Maruyama et al. Mutations of optineurin in amyotrophic lateral sclerosis. Nature 465, 223–226.

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Highly Penetrant *RAD51C* Mutations Found in Families with Hereditary Breast and Ovarian Cancer

Although *BRCA1* and *BRCA2* are the most famous, and most commonly mutated, genes involved in hereditary breast and ovarian cancer (HBOC), they belong to a group of genes encoding participants in the homologous recombination pathway of DNA repair, of which several have been implicated in cancer predisposition and in Fanconi anemia. Not all HBOC families have a mutation in the known disease genes in this complex, however, leading to further investigation of its members. These explorations have recently implicated *RAD51C* as an additional gene associated with HBOC and Fanconi anemia. Vaz et al. used homozygosity mapping in a consanguineous family with a Fanconi-anemia-like phenotype to identify a homozygous missense mutation in *RAD51C* in affected individuals, who are also shown to have an aberrant response to DNA damage. On the basis of this finding, Meindl et al. looked for heterozygous *RAD51C* mutations in women from families with hereditary breast or both breast and ovarian cancer in whom no *BRCA1* or *BRCA2* mutation had been found. They discerned six novel pathogenic *RAD51C* mutations that were limited to families with both breast and ovarian cancer. In fact, 1.3% of these families had a *RAD51C* mutation, and the penetrance of these mutations was substantial. Although these mutations are not as common as those in *BRCA1* or *BRCA2*, they would have significant implications for HBOC families in whom no causative mutation has yet been found.

Vaz et al. Mutation of the RAD51C gene in a Fanconi anemia-like disorder. Nature Genetics 42, 406–409.

Meindl et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nature Genetics 42, 410–414.

Sometimes Too Much of a Good Thing Can Be as Bad as Too Little

The proteins encoded by the mitochondrial genome are crucial for oxidative phosphorylation and, thus, for cellular survival. Although we know that many copies of the mtDNA exist per cell, the fact that a substantial fraction of them need to contain a mutation before you see an observable defect in respiratory activity could mean that there is leeway in the number of copies of mtDNA that a cell needs. Not so, according to two recent studies that used transgenic mouse models to explore the regulation of mtDNA level and found that too much or too little mtDNA per cell can actually be detrimental. Ylikallio et al. overexpressed the mitochondrial transcription factor TFAM and/or the mitochondrial DNA helicase Twinkle in mice. These mice have increases in mtDNA copy number, alterations to the content and size of the clusters of mtDNA, known as mitochondrial nucleoids, and reductions in mitochondrial transcription. Chen et al., on the other hand, deleted two genes critical for mitochondrial fusion, *Mfn1* and *Mfn2*, specifically in skeletal muscle. In this case, the mice showed decreases in mtDNA copy number, mitochondrial proliferation, and muscle atrophy. Although the two sets of mice have mtDNA copy number alterations in opposite directions, both had mitochondrial dysfunction and were found to accumulate mtDNA deletions in the affected tissues, indicating a fairly tight regulation of mtDNA copy number, mtDNA integrity, and mitochondrial function.

Chen et al. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. Cell 141, 280–289.

Ylikallio et al. High mitochondrial DNA copy number has detrimental effects in mice. Human Molecular Genetics. Published online April 22, 2010. 10.1093/hmg/ddq163.

This Month in Our Sister Journals

How Much Do You Want to Know?

As genotyping arrays assess more and more SNPs for each individual in a research study, it becomes increasingly likely that the study participants will be tested for genetic variants that have direct or indirect health implications. Johnson et al. explored the notion that for some genetic variation there may be compelling reasons to recontact study participants to notify them of their genotype status. They researched the status of currently available genotyping arrays by comparing the SNPs on 18 different formats with the GeneTests databases, looking for disease-causing variants that are specifically tested in CLIA-certified labs. They also used data from the Framingham Heart Study to assess the likelihood of finding potentially reportable genotypes in a large genome-wide association study. Twelve SNPs representing nine genetic diseases were found on currently available commercial SNP arrays, with an additional four that were in complete linkage disequilibrium with disease variants. However, further analysis indicated that, for most of these SNPs, compelling evidence was lacking to suggest that the results be reported back to study participants. This was largely due to reduced or unclear penetrance, the fact that the disorders of concern would be detected through newborn screening, or a lack of strong evidence for clinical intervention as a result of identifying the variant. The most compelling candidate for reporting was the predominant mutation that causes hereditary hemochromatosis, and further evaluation of this variant as a potentially notifiable finding is suggested.

Johnson et al. CLIA-tested genetic variants on commercial SNP arrays: potential for incidental findings in genome-wide association studies. Genetics in Medicine. Published online May 17, 2010. 10.1097/GIM.0b013e3181e1e2a9.

Back to Basics

Measuring gene expression via RNA sequencing with the use of next-generation technologies is the latest way to look globally for gene-expression differences between samples. Let's say, though, that you've got two samples to compare: you extract RNA, prep it, and run the two samples side by side on the flow cell. How much of the variation between the two samples is due to a true biological difference, and how much is due to the fact that the samples were prepared and run separately? This is the problem that Auer and Doerge are trying to avoid in their paper on the design and analysis of this type of data. They go back to basic experimental-design principles proposed by R. A. Fisher in the 1930s and discuss how these principles can be used with RNA sequencing experiments for gene expression. They leverage the properties of the sequencing format, which allows for multiplexing through the use of genetic bar coding of samples, meaning that multiple samples can be prepped and run together in a design that can reduce technical confounding variables. They use simulations to compare the performance of various experimental and statistical designs. Sure, we can produce reams and reams of data in one go with the latest technologies, but unless we go back to the basics of the scientific method, all of this data could be meaningless.

Auer and Doerge. Statistical design and analysis of RNA-Seq data. Genetics. Published online May 3, 2010. 10.1534/genetics.110.114983.